Remarks

Introduction

The above-identified application has been carefully reviewed in light of the Office Action mailed January 15, 2004, which included a final rejection of the pending claims. Applicant submits that the remarks included herein show the present claims to be allowable and do not raise new issues. Therefore, applicant respectfully requests that this request for reconsideration be entered.

As a preliminary matter, applicant acknowledges that the previous rejections of claims 1-9 and 17-26 under 35 U.S.C. § 112, second paragraph have been withdrawn. The only outstanding rejection is a rejection of the present claims under 35 U.S.C. § 103.

Status of Claims

Claims 1-9, 17-26, and 28-29 are currently pending.

Summary of Invention

The present invention generally relates to a method of treating patients by simultaneously administering two or more botulinum neurotoxins to a patient (claims 1-9) and a composition comprising a combination of at least two botulinum neurotoxins (claims 17-26 and 28-29). In other words, claims 17-26 and 28-29 are directed to at least two botulinum neurotoxins provided in a single composition. Such a composition may be administered to a patient resulting in the simultaneous administration of two or more botulinum neurotoxins. Two specific combinations of botulinum neurotoxins

are described in claims 28 and 29 (A and B, and A and E, respectively).

Rejections Under 35 U.S.C. § 103

Claims 1, 6, 17, 22, and 26-27 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ludlow et al. in view of Schantz et al.; Ludlow et al. in view of Tsui et al.; and Ludlow et al. and Shantz et al. in view of Sugiyama. Claims 1-9 and 17-29 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Ludlow et al. and Shantz et al. in view of Sugiyama.

Applicant respectfully traverses the rejections as they apply to the present claims.

To establish a *prima facie* case of obviousness, three basic criteria must be met (MPEP 2143). First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify a primary reference or to combine reference teachings. Second, there must be a reasonable expectation of success that the suggested combination will work. Third, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in Applicant's disclosure (*In re Vaeck*, 947 F.2d 488, (Fed. Cir. 1991)). Hindsight reconstruction cannot be used to pick and choose from among isolated disclosures in the prior art to deprecate the claimed invention (*In re Fine*, 837 F.2d 1071, 1075, (Fed. Cir. 1988)).

Applicant again submits that the rejections are in error, and that the Examiner has not met the burden of proof of establishing a *prima facie* case of obviousness.

For example, the Office Action fails to indicate where in the prior art a suggestion or motivation is provided to modify the teachings of the references to obtain the claimed methods and compositions, which recite compositions containing a combination of two or more specific neurotoxins. The motivation or suggestion to support a rejection under 35 U.S.C. § 103 must be clear and particular (*In re Dembiczak*, 175 F.3d 994, 999, 50 USPQ2d 1614, 1617 (Fed. Cir. 1999); emphasis added), and "particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed" (*In re Kotzab*, 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000)).

Applicant respectfully submits that the prior art fails to provide any showing, let alone the requisite clear and particular showing, that one of ordinary skill in the art would have been motivated to modify the teachings of the references to obtain the claimed compositions or methods. Absent such a clear and particular indication, the rejections under 35 U.S.C. § 103 cannot be maintained.

In addition, even if the references were to be erroneously combined, the combination fails to disclose, teach, or even suggest all of the limitations recited in the present claims.

For example, the combination of references does not disclose, teach, or even suggest a method comprising a step of simultaneously administering at least two botulinum neurotoxins to a patient, as recited in claims 1-9; or a composition

comprising at least two botulinum neurotoxins as recited in claims 17-26 and 28-29.

In addition, the combination of references fails to disclose, teach, or even suggest a method or composition in which each selected neurotoxin is present in an amount selected to control a duration of therapeutic activity of the combination of neurotoxins, as recited in claims 1-7 and 17-26, or the specific combination of botulinum toxin type A and botulinum toxin type B, as recited in claim 28, or the specific combination of botulinum toxin type A and botulinum toxin type E, as recited in claim 29.

Thus, because the Examiner has failed to indicate where in the prior art there is a clear and particular showing that one of ordinary skill in the art would be motivated to combine the references, and because no combination of the references discloses, teaches, or suggests all of the limitations of the present claims, applicant submits that a *prima facie* case of obviousness has not been established.

In maintaining the rejections, the Examiner appears to be relying on the statement that "there is nothing on the record to show that the combination of teachings would not suggest the claimed invention" (see Office Action, page 3, penultimate paragraph; page 5, last paragraph; page 7, first full paragraph; and page 8, last paragraph).

Applicant submits that the burden of proof does not shift to the applicant until the Patent Office has established a *prima facie* case. Applicant respectfully submits that it is well established and understood that the burden of proof only shifts to the applicant after the Patent Office presents a *prima facie* case of obviousness (*In re Rijckaert*, 28 USPQ2d 1955, 1956 (Fed.

Cir. 1993) citing *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); emphasis ours).

In the present situation, the burden of proof does not shift to the applicant until the Patent Office has established that the present claims are *prima facie* obvious over the prior art. Only after the Patent Office has established a *prima facie* case, does the burden shift to the applicant to demonstrate that the combination of references would not suggest the present invention. Because the Examiner has not established a *prima facie* case, the burden remains with the Examiner to demonstrate that the claimed invention is obvious over the combination of references.

In addition, the Examiner continues to state that it would have been obvious to one of ordinary skill in the art at the time of the invention to combine two compositions each containing a single neurotoxin based on the "idea that combining them flows logically from [single neurotoxins] having been individually taught in the prior art," or "the substitution of one [neurotoxin] for the other would be readily expected to work given that two of the individual neurotoxins have been individually shown to be effective for the treatment of torticollis." The Examiner appears to be of the opinion that because the references teach pharmaceuticals containing only one type of botulinum toxin, and that seven different types of botulinum toxin were known, it would have been obvious to one of ordinary skill in the art at the time of the invention to include two or more botulinum toxins in a single composition.

However, as acknowledged in the Office Action, none of the references disclose, teach, or even suggest a composition comprising at least two types of botulinum toxins, or the use thereof (see page 2, sixth and seventh paragraphs; page 4, third

and fourth full paragraphs; and page 6, second and third paragraphs). Even if the combination of references may suggest that a second botulinum neurotoxin can be administered after (i.e., not simultaneously) a different first botulinum neurotoxin ceases to be therapeutically effective, such sequential administration does not make obvious the present claims. In fact, such sequential administration of one botulinum neurotoxin followed separately by administration of a different single botulinum neurotoxin clearly, directly, and expressly teaches away from the present invention in which two or more different botulinum neurotoxins are simultaneously administered, or in which two or more different botulinum neurotoxins are provided in one composition.

Furthermore, applicant submits that the references alone, or in combination, do not disclose, teach, or even suggest, compositions which contain a combination of at least two different botulinum toxins, each botulinum toxin being present in an amount selected to control a duration of therapeutic activity of the combination of neurotoxins, as recited in claims 1-9 and 17-26. In fact, not only are the references silent as to compositions containing a combination of different botulinum toxins, the references are expressly silent with respect to any specific amount of toxins used in such a composition, let alone, amounts that are effective to control a duration of therapeutic activity. Thus, because the references individually do not disclose, teach, or even suggest, a composition comprising a combination of different botulinum toxins in specific amounts, as recited in the claims, the reference combination contended by the Examiner fails to recite all of the limitations recited in the pending claims, and in particular claims 1-9, and 17-26.

Similarly, the references alone or in combination do not disclose, teach, or even suggest any specific combinations of individual neurotoxins, let alone the specific combination of botulinum toxin type A and botulinum toxin type B, as recited in claim 28, or the specific combination of botulinum toxin type A and botulinum toxin type E, as recited in claim 29.

The Brin Declaration Rebuts the Obviousness Rejection

Although the burden remains with the Examiner to establish a *prima facie* case of obviousness, to advance the prosecution of the subject application, applicant submits herewith, as Exhibit A, a copy of the February 8, 2001 declaration of Dr. Mitchell Brin (hereinafter, the "Brin Declaration"). The original of the Brin declaration was submitted in application U.S. Serial Number 09/490,756 with the response dated February 16, 2001.

Dr. Brin is an acknowledged expert in the use of botulinum toxin for treating neuromuscular disorders, such as dystonia. The Brin Declaration is being submitted as further evidence of the patentability of the present claims.

Decisions from the courts, which review Patent Office decisions, are instructive as to the deference and weight to be accorded the evidence presented in the Brin Declaration. An expert opinion expressed in a Declaration can overcome an obviousness rejection: "The expert opinion was introduced on the issue of the level of ordinary skill ... the prima facie case of obviousness has been overcome", and the Examiner's obviousness rejection was reversed. *In re Oelrich and Divigard*, 579 F.2d 86, 198 USPQ 210 at 215 (CCPA 1978).

Additionally, in *In re May and Eddy*, 574 F.2d, 197 USPQ 601 (CCPA 1978), four declarations were submitted in response to an obviousness rejection. The Court relied heavily upon the

affidavit from an expert in the field (the Jackson affidavit) which stated that the claimed method of affecting analgesic and morphine antagonistic activity through use of a particular compound "was unexpected and unpredictable" since the property of the compound used in the method to affect analgesic and morphine antagonistic activity "had not previously been established." (197 USPQ at 606) (emphasis added). The Court concluded based in large part upon the Jackson affidavit (see 197 USPQ 608, paragraph [6]) that the method claims were not obvious, and reversed the Examiner's obviousness rejection. *In re May and Eddy* is directly applicable here since the present claims include method claims (a method of treating a patient suffering from a neuromuscular disorder or condition), which use a particular compound (botulinum toxin).

Applicant submits herewith the Brin Declaration as evidence that the prior art references of the above-identified application do not disclose, teach, or even suggest the presently claimed invention.

For example, paragraph 6 of the Brin declaration states: "As of the April 25, 1991 date of the Jankovic reference, it was **completely unknown** as to whether or not botulinum toxin type B would have any therapeutic efficacy in humans. Indeed, as far as I am aware, the first reported use of type B botulinum toxin in humans did not occur until 1995" (emphasis added).

Additionally, paragraph 8 of the Brin declaration states: "In my opinion, prior to December 28, 1993, it would have been **foolhardy and dangerous** to use botulinum toxin type B to treat patients with dystonia, such as cervical dystonia, in light of clinical experience with the type B toxin as of that date" (emphasis added).

The present application has an effective filing date of June 10, 1993 (i.e., prior to December 28, 1993). Therefore, as of the effective filing date of the above-identified application, it is Dr. Brin's opinion that the use of botulinum toxin type B, alone, would have been **foolhardy and dangerous**. Clearly, based on that statement, a person of ordinary skill in the art would conclude that it would also have been **foolhardy and dangerous** to simultaneously administer two or more botulinum neurotoxins (e.g., botulinun toxin types A and B) to a patient, or provide two or more botulinum toxins in a single composition. As identified in the above-identified application (page 1, lines 16-18), botulinum neurotoxin is considered to be the most deadly poison known. Applicant submits that it would not be obvious to combine different botulinum neurotoxins, the most deadly poison known, into a simultaneous administration step or into a single composition to treat patients based on the prior art references.

In view of the above, applicant submits that the present claims 1-9 and 17-26 and 28-29 are unobvious from and patentable over Ludlow et al., Shantz et al., Tsui et al., and Sugiyama et al., alone or in any combination, under 35 U.S.C. 103(a).

Each of the present dependent claims is separately patentable over the prior art. For example, none of the prior art disclose, teach, or even suggest the present methods and compositions including the additional feature or features recited in any of the present dependent claims, such as the specific combinations of neurotoxins. Therefore, applicant submits that each of the present claims is separately patentable over the prior art.

In conclusion, applicant has shown that the present claims satisfy the requirements of 35 U.S.C. § 112, and are unobvious from and patentable over the prior art under 35 U.S.C. § 103.

Therefore, applicant submits that the present claims, that is claims 1-9, 17-26, and 28-29 are allowable. Therefore, applicant requests the Examiner to pass the above-identified application to issuance at an early date. Should any matters remain unresolved, the Examiner is requested to call (collect) applicant's attorney at the telephone number given below.

Respectfully submitted,

Date: March 12, 2004

Frank J. Uxa
Attorney for Applicant
Registration No. 25,612
4 Venture, Suite 300
Irvine, California 92618
(949) 450-1750
(949) 450-1764 Facsimile